PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P045081PCT BSW/jdO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL 03/00127	20.02.2003	20.02.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K38/00		
Applicant		
ACADEMISCH ZIEKENHUIS BIJ DE UNIVERSITEIT ...et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.08.2003	26.05.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL 03/00127

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-44 as originally filed

Claims, Numbers

1-29 as originally filed

Drawings, Sheets

1/13-13/13 as originally filed

Sequence listing part of the description, pages:

45-49, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-27

   because:

   ☒ the said international application, or the said claims Nos. 1-13,25-27 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-24

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-5,7-9,17-20,22-27
	No:	Claims	1,6,10-16,21,28-29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	see separate sheet
	No:	Claims	

2. Citations and explanations

see separate sheet

Re item III

Non-establishment of opinion

1. Claims 1-13, 25-27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

The applicant's attention is drawn to the fact that for the assessment of the said claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2. Claims 1-24 have been objected by the international search authority under Article 5 PCT and Article 6 PCT. The international preliminary examination is limited accordingly.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO-A-9920298
D2: US-B-6 271 363 (INGHAM PHILIP W ET AL) 7 August 2001 (2001-08-07)
D3: WO 01 98344 A (BIOGEN INC ;LING LEONA E (US); SANICOLA NADEL MICHELE (US)) 27 December 2001 (2001-12-27)

1 NOVELTY (Art. 33(2) PCT)

1.1 The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of claims 1,6,10-16,21,28-29, insofar as clear and patentable, is not new in respect of the prior art as defined in the regulations (Rule 64(1)-(3) PCT):

1. Document D1 discloses a method and use of a Hedgehog protein for the

treatment of gastrointestinal diseases (e.g. ulcerative colitis, mucositis, peptic ulcer disease, gastroenteritis and, vilus atrophic disorders) in patients in need of such treatment. In addition document D1 discloses a gene therapy construct encoding a hedgehog polypeptide. Furthermore an enteric bacterium (E. coli) comprising a nucleotide sequence encoding a Hedgehog protein is described wherein the vectors enlisted can confer the bacterium to secrete the Hedgehog protein (pBR322, pEMBL-, pEX, pBTac- and pUC-derived plasmids)(cf. ; page 4, lines 5-18; page 5, lines 5-8; page 8, lines 26-28; page 20, lines 4-15; page 39, lines 21-23).

Therefore, the subject matter of claims 1,6,10-16,21,28-29 is not new (Article 33(2) PCT).

1.2 The applicant intends to express claims 14-16,21 in the so called second medical use form. For the novelty examination, the concept of second or further medical use can only be applied to claims to the use of substances or compositions for the preparation of a medicament intended for use in a new therapeutical apllication. The feature "a deficiency of hedgehog protein in the GI tract" does not necessarily reflect a disease to be treated. Variations in the expression patterns of proteins among individuals/groups of the human population can exist without necessarily leading to disease (e.g. pigmental proteins are expressed to varying extents among the human populations). The said feature of the claims cannot therefore be considered to represent a further medical indication from which novelty could be derived. Consequently, the novelty of the subject-matter of claims 14-16,21 is anticipated by the disclosure of document D2 (cf. summary of invention) which discloses hedgehog protein in therapy (first medical use)(Article 33(2) PCT).

2 **INVENTIVE STEP (Art. 33(3) PCT)**

2.1 The problem to be solved by the present invention is the treatment of GI tract diseases, in particular GI tract cancer by administration of Hedgehog protein/gene. The document D3 discloses over expression of Hedgehog protein in several human gastrointestinal tumour cell lines (example: T84 (human colon epithelial carcinoma, CCL-284, ATCC, Manassas, VA); Caco2 and SW480 (human colon epithelial adenocarcinomas, HTB-37 and CCL-228, ATCC, Manassas, VA) compared to normal human gastrointestinal epithelial cells or

fibroblasts and further discloses that inhibition of hedgehog using, for example, anti-hedgehog blocking antibody decreases tumour growth rate and/or tumour angiogenesis (cf. page 102, lines 21-23; page 104, lines 16-18; example 7). In view of document D3 the examining division is not convinced that the problem is solved by the invention. Therefore, as the subject-mater of the present application does not exhibit the claimed therapeutic effect in a credible manner, an inventive step cannot be acknowledged for the present application (Article 33 (3) PCT). To overcome this objection, the applicant is requested to provide arguments and experimental evidence which explain the discrepancy between the disclosure of D3 and the subject matter of the present invention.

VII Certain observations

1. The claims 1,6,7,10-16, 21,22 are related to the prevention or treatment of diseases which are not clearly defined, namely conditions related to "a deficiency of a hedgehog protein in the GI tract" or "suffering from deficiency". Due to the functional definition of the claimed subject-matter, the scope of protection of the claims 1,6,7,10-16, 21,22 is obscure and not limited to the treatment of said specified conditions in the description and/or the claims but, by contrast, embraces an undefined number of other conditions allegedly capable of being improved or prevented by the administration of Hedgehog protein. Therefore, the claims 1,6,7,10-16, 21,22 lack support (Art. 6 PCT) and the application lacks disclosure (Art. 5 PCT). Independent of the above reasoning the expressions "a deficiency of a hedgehog protein in the GI tract", "source", and "suffering from deficiency" are vague and unclear and leave the reader in doubt as to the mean ing of the technical feature to which they refer, thereby rendering the definition of the subject-matter of claims 1,6,7,10-16, 21,22 unclear (Article 6 PCT).

Furthermore, the applicant's attention is drawn to the fact that the mechanism of action of a drug (method for treating a deficiency of a Hedgehog protein in the GI tract) cannot be considered in itself as a therapeutic application; the discovery that a substance has a particular pharmacological profile still needs to find a practical application in the form of a defined real treatment of a pathological condition.

2. The term "ectopic gastric tissue" in claim 27 is unclear and leaves the reader in

doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

3. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1-3 is not mentioned in the description, nor are these documents identified therein.